

Report of Shmuel Shoham, M.D. Regarding Box Hill Surgery Center Clinic Patient Fungal Infection Outbreak

I have been asked to provide expert opinion on behalf of John C. Millhausen, Edna C. Young, Teresa A. Davis, Belinda L. Dreisch, Angela Farthing, Bahman Kashi, Linda J. Torbeck and Brenda Lee Rozek, patients treated at Box Hill Surgery Center by Ritu Bhambhani, M.D. in 2012, regarding the outbreak of fungal meningitis and other infections caused by injections of contaminated, purportedly preservative free methylprednisolone acetate solution (PF-MPA) produced by New England Compounding Center (NECC). In this report I will describe pertinent causes of the outbreak, its course, and the infectious complications that, to a reasonable degree of medical probability, arose in patients, a number of which were in Maryland, from exposure to the contaminated PF-MPA.

I have also been asked for my opinion as a licensed physician in Maryland on whether the method and manner in which PF-MPA from NECC was prescribed, ordered and administered at Box Hill Surgery Center by Dr. Bhambhani conformed to the standards of care for doctors in Maryland on prescribing and administering prescription medications to patients.

Professional Qualifications:

I am an Associate Professor of Medicine at Johns Hopkins University School of Medicine and Associate Director of the Transplant and Oncology Infectious Diseases program at that institution. I am certified by the American Board of Internal Medicine in Internal Medicine and in Infectious Diseases, and am licensed to practice medicine in the State of Maryland and the District of Columbia. I have over 15 years of experience in management of patients with invasive fungal infections, and am the author or co-author of over 90 original articles, book chapters and topic reviews, including publications directly related to the fungal infection outbreak associated with the contaminated PF-MPA injections. I serve as a reviewer and expert consultant to multiple journals, professional societies and government agencies in the US and abroad and am a member of professional guideline committees for the American Society of Transplantation (AST), the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and Infectious Diseases Mycoses Study Group (EORTC/MSG) and the National Comprehensive Cancer Network (NCCN). In 2015 the Washington, DC Chapter of the American College of Physicians honored my commitment to excellence in medical care and service to the College with their highest award, the John F. Maher Memorial Laureate Award. Attached is my *Curriculum Vitae*, which includes a list of publications I have authored.

Prior Expert Testimony:

In the past 4 years I have testified as an expert by deposition (on August 11, 2016) in the case of Barbara J. Bradley vs. David J. Sugarbaker (United States District Court, District of Massachusetts). During this period I have not testified as an expert at trial.

Summary of outbreak

Overview

Starting in 2012, patients across the US, including Brenda Rozek, Belinda Dreisch, and over 20 others in Maryland were part of an outbreak of fungal infections associated with injections of PF-MPA from NECC. The predominant microbial culprit was *Exserohilum rostratum*, a fungus typically found in soil and on plants. The PF-MPA was from lots contaminated by this, and perhaps additional fungi. The contaminated product was produced by NECC in Framingham, MA and shipped to medical facilities across the US. The ultimate outcome was hundreds of cases of spinal and central nervous system infection and, according to the Center for Disease Control (CDC) case counts, 64 deaths, including 3 in Maryland. (As the testimony of Dr. Lucy Wilson beginning at page 202 of her deposition representing the Maryland Department of Health and Mental Hygiene (DHMH)¹ reveals, there actually were four deaths attributable to NECC PF-MPA injections in Maryland, all of whom were Box Hill Surgery Center patients. Bahman Kashi's death was categorized in CDC's case counting as being a California case). All in all, this was one of the largest outbreaks of health care associated infections and the largest outbreak of fungal meningitis documented in the US.

From NECC to patients

Between May and September of 2012, over 17,000 vials from 3 fungal contaminated PF-MPA lots (05212012@68, 06292012@26, and 08102012@51) produced by NECC were distributed to multiple medical facilities across the US. These included Box Hill Surgical Center as well as several others in Maryland. The PF-MPA from these contaminated lots was then used for injections in about 13,500 patients across the United States. The vast majority (~90%) received injections into the epidural,

¹ Dr Wilson is the Chief of DHMH's Center for Surveillance, Infection Prevention and Outbreak Response. She was in charge of DHMH's investigation of the 2012 fungal infection outbreak.

spinal, or paraspinal regions.

The manner by which the contaminated steroids reached patients did not always conform to the standards of care. A specific example is the method and manner in which PF-MPA from NECC was prescribed, ordered and administered at Box Hill Surgery Center in Maryland.

Under Maryland's law applicable to prescribing prescription medicines, as well the applicable standards of care on prescribing and administering prescription medications, a doctor must prescribe a prescription medication that is to be filled and dispensed by a pharmacy – which includes compounding pharmacies when prescribing a compounded medication – only for a specific patient that he or she is treating and for a specific medical need of that particular patient. Additionally, once a prescription medication is dispensed with a label identifying it as prescribed for a specific patient, a doctor (or clinical staff at his or her direction) may not, transfer that medication and administer it to a different person or patient.

Based upon the testimony of Dr. Bhambhani and Nurse Andrew Vickers, it is my opinion that these standards of care were not followed. Specifically, NECC's PF-MPA was prescribed on NECC prescription order forms, with multiple vials ordered per patient, for patients who had already undergone treatment at Box Hill. The PF-MPA vials were subsequently dispensed by NECC and received by Box Hill with labels bearing the names of patients listed on the NECC prescription order form. PF-MPA from the vials was then administered to other patients not listed on the prescription form or on the medication labels.

From Injections to Infections

Injection of fungal contaminated PF-MPA into patients' deep tissues resulted in many patients developing infections at those sites of injection and/or in surrounding structures. These included catastrophic cases where the central nervous system became involved.

Under normal circumstances, patients are protected from fungal infections by intact tissue barriers that prevent fungal cells from gaining access to sterile body sites. Once a fungus has penetrated through normal tissue barriers and starts to grow it can cause extensive damage including destruction of normal tissues and even death. Steroids can further exacerbate the situation by accelerating the growth of fungi such as *Exserohilum rostratum* and impairing the immune system's ability to control their growth. The damage may occur right away or take many weeks (or even longer) to become manifest. Steroids may mask this process while it is happening leading to delays in diagnosis. Because anatomical barriers to infection can be damaged by surgery, or bypassed altogether when medicines are directly injected into sterile sites, extreme care must be taken to prevent fungal contamination during such procedures. This is even more crucial in patients who are receiving

corticosteroids.

Starting in July of 2012, patients across the country began to develop infections related to the injections. The first to be documented was a spinal region infection in July 2012. However, a connection to the contaminated lots was not made until September of that year, when the Tennessee Department of Health was alerted by a physician that a patient in Nashville had died of culture-confirmed fungal meningitis, and that this patient had received an epidural steroid injection 46 days earlier. The contaminated lots of PF-MPA were recalled, but by then an estimated 13,534 patients across the US, including many in Maryland, had already received injections with the potentially contaminated product.

Management of the Infections and outcomes

Using Centers for Disease Control and Prevention (CDC) criteria developed specifically for the outbreak by infectious disease and other experts, 753 patients across the US were ultimately discovered to have infections related to the PF-MPA injections. The incubation period was typically about 6-7 weeks, but in some patients infection was only discovered many months after their injections. Nearly all of those developing infections had meningitis and/or infections in nearby structures. These included infection and inflammation of the spine itself, the epidural region and the nerve roots. Exposed patients had strokes when the blood vessels of the brain were involved. Establishing the diagnosis typically required invasive procedures such as spinal taps and tissue biopsies. A small minority (<5%) developed infections in peripheral joints.

These injuries and outcomes are fully consistent with generally accepted medical knowledge on the effects of fungal infections. The cause and effect association is clear and when asked about the etiology of specific death cases investigated by DHMH where the administration of contaminated NECC PF-MPA occurred at Box Hill, DHMH's Dr. Wilson, concluded that the four deaths among Box Hill patients were confirmed cases of NECC steroid fungal infection. Deposition Transcript of Lucy Wilson, M.D. at pgs. 183-185, 202-217.

Treatment of exposed patients was often long, difficult and not always successful. Most patients received about 6 months of antifungals, which were usually with voriconazole and/or amphotericin B. Some required longer courses. Patients receiving voriconazole often developed side effects such as liver toxicity, hallucinations and visual disturbances, while those receiving amphotericin B often developed acute kidney injury and some even required dialysis. Many patients with spinal region infections required back surgery to decompress neural elements, remove infectious material, and obtain tissue for diagnostic purposes. Those with peripheral joint infections typically underwent procedures such as incision and drainage, washout, bursectomy, or total arthroplasty. Some patients, as noted above, died.

Conclusions and outlook for the future

This tragic outbreak involved at least 753 patients and caused 64 deaths nationwide according to the CDC counts. In Maryland there were 26 cases (almost all with meningitis) and 4 deaths attributable to the outbreak (including the fourth Box Hill patient's death Dr. Wilson confirmed at her deposition). The medical community's response to this outbreak required the efforts of thousands of clinicians and public health officials at federal, state, and local levels. Patients suffered significant injuries from the infection and its therapy, and in a number of cases died as a result of their infections. It is not known what the future holds for those patients who appear to have cleared the infection. For example, will infection return in patients who have stopped antifungal therapy? Instances of relapse have been reported, including one patient whose infection recurred 21 months after cessation of therapy, prompting CDC experts to warn clinicians and patients that they "should remain watchful for symptoms of infection in patients exposed to the contaminated PF- MPA, because fungal infections can develop slowly and are difficult to eradicate".

Documents Reviewed for this Report:

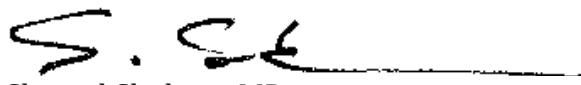
1. Maryland Department Health and Mental Hygiene medical files, test reports and spreadsheets on Box Hill Surgery Center patients administered NECC MPA-PF at Box Hill during procedures.
2. Lyons, Jennifer L., et al, *Fatal Exserohilum Meningitis and Central Nervous System Vasculitis After Cervical Epidural Methylprednisolone Injection*, Annals of Internal Medicine 157:11, p.835 (Dec. 4, 2012) (Brenda Rozek case report).
3. Smith, Rachel M., et al, *Fungal Infections from Contaminated Methylprednisolone*, New England J. of Med. 369;17, p. 1598 (Oct. 24, 2013).
4. Tom M. Chiller, *Clinical Findings for Infections from Methylprednisolone Caused by Methylprednisolone Injections*, New England J. of Med. 369;17, p. 1610 (Oct. 24, 2013).
5. Wilson, Lucy E., et al., *Fungal Meningitis From Injection of Contaminated Steroids: A Compounding Problem*, J. American Medical Association, 308:23 p 2481(Dec.19, 2012).
6. Deposition transcript of Dr. Ritu Bhamhani, M.D.
7. Bhamhani Deposition Exhibits Nos. 1062, 1063, 1064 and 1065.
8. Deposition transcript of Nurse Andrew Vickers, R.N.
9. Vickers Deposition Exhibits Nos. 1148, 1149 and 1150.
10. Deposition transcript of Dr. Lucy Wilson, M.D.
11. Copies of Box Hill's NECC Prescription Orders forms used to obtain MPA-PF by mail order and packing slips from NECC.
12. Maryland Statute on prescription requirement (MD. Health Code Section 21-220.
13. Board of Pharmacy Newsletter – Fall, 2012.

14. Kauffman CA, Malani AN. *Fungal Infections Associated with Contaminated Steroid Injections*. Microbiol Spectr. 2016;4(2).
15. Pettit AC, Malani AN. *Outbreak of fungal infections associated with contaminated methylprednisolone acetate: an update*. Curr Infect Dis Rep. 2015;17(1):441.
16. Moudgal V, Singal B, Kauffman CA, Brodkey JA, Malani AN, Olmsted RN, et al. *Spinal and paraspinal fungal infections associated with contaminated methylprednisolone injections*. Open Forum Infect Dis. 2014;1(1):ofu022.
17. Casadevall A, Pirofski LA. *Exserohilum rostratum fungal meningitis associated with methylprednisolone injections*. Future Microbiol. 2013;8(2):135-7.
18. Simitopoulou M, Walsh TJ, Kyripiti D, Petraitis V, Kontoyiannis DP, Perlin DS, and Roilides E. Methylprednisolone impairs conidial phagocytosis but does not attenuate hyphal damage by neutrophils against *Exserohilum rostratum*. *Medical Mycology*, 2015, 53, 189–193.
19. Farmakiotis D, Shirazi F, Zhao Y, Saad PJ, Albert ND, Roilides E, Walsh TJ, Perlin DS, and Kontoyiannis DP. *Methylprednisolone Enhances the Growth of Exserohilum rostratum In Vitro, Attenuates Spontaneous Apoptosis, and Increases Mortality Rates in Immunocompetent Drosophila Flies*. The Journal of Infectious Diseases 2014; 210:1471–5.

My fee for research, writing, consultations and testimony at deposition and trial in the cases at issue is \$500 per hour.

I reserve the right to supplement, modify or amend this letter report after further research and review of additional material, including depositions.

Respectfully submitted,



Shmuel Shoham, MD

Dated: September 14, 2016